Multi-Cancer Early Detection Tests and Modeling the Potential Impact on Insurance

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Summary

What are multi-cancer early detection tests?

A liquid biopsy (LB), as opposed to a traditional tissue biopsy, is a new class of test which looks for biological signals or markers of possible cancer or other non-cancer entities in a person's bodily fluids – most often in blood, but also in urine, saliva, cerebrospinal fluid, or other non-invasive, more easily accessible body fluid. A multi-cancer early detection (MCED) test is a LB able to detect multiple cancers with a single blood draw, using genomic sequencing or biochemical analysis in combination with machine learning that aims to shift the diagnosis of cancers to an earlier stage. MCED tests also detect multiple cancers where screening tests are currently unavailable, challenging contemporary cancer screening paradigms in terms of efficiency, accessibility, and affordability.

Why is this important?

At present, traditional screening tests detect only a limited number of cancers, for example, mammograms for the early detection of breast cancer. The majority of cancer deaths are due to cancers with diagnoses occurring following investigation into patient signs or symptoms, which can already be at a late stage and result in poorer survival and mortality outcomes. From one single blood draw, MCED tests can identify up to 50 or more different cancer types earlier than they are currently diagnosed and at potentially earlier stages, thus improving mortality and morbidity outcomes.

How do MCED tests likely impact mortality and morbidity assumptions?

MCED tests represent a breakthrough in medical science, and if this technology continues to develop cost-effectively, the impacts will be seen

over the medium to long term as use increases. This should include reduced mortality as cancers are diagnosed at earlier stages, and improvements in life expectancy as cancer is one of the leading causes of death in developed countries. However, MCED tests also will bring increased diagnosis of cancers at younger ages and some overdiagnosis, increasing cancer morbidity rates. Quantifying potential outcomes is difficult, given the many uncertainties at play; however, the long-term nature of many insurance contracts makes it imperative to develop models to assess this emerging medical technology's potential impact on future mortality and morbidity assumptions. To this end, RGA recently developed a model to assess the potential impact of MCED tests, revealing significant potential impacts on cancer incidence and mortality rates.

Introduction

What is a liquid biopsy, what are its uses, and how could it be used in MCED testing?

A liquid biopsy (LB) is a fluid-based biomarker test to aid in disease detection. Different types of LBs detect different biomarkers, including:

- Circulating cell-free DNA (cfDNA) – fragments of DNA that are routinely shed into the blood by all cells in the body
- Circulating tumor DNA (ctDNA) – cfDNA that is shed specifically by tumor cells
- Exosomes – tiny, extracellular vesicles that contain genetic material and other molecules
- Circulating tumor cells (CTCs) – intact, whole tumor cells that are shed into the blood by the larger tumor mass

One advantage of CTC analysis is that it allows for complete assessment of both tumor DNA and tumor RNA, enabling analysis of the transcriptome, which is translated into the final protein product of a cell. Interestingly, CTCs were observed in a patient with metastasis as early as 1869,[1] but the FDA only approved the first liquid biopsy CTC test in 2004.[2]

Several clinical applications of LB testing exist. Non-cancer clinical applications include use in organ transplant monitoring to detect graft dysfunction, as cell counts in the blood can increase during organ rejection.

LBs also can be used for organ damage assessment after myocardial infarction or in autoimmune disease monitoring. Non-invasive prenatal testing (NIPT), which measures fetal circulating free DNA in the mother's blood, has been used globally for the screening of fetal chromosomal aneuploidies (such as Down syndrome or trisomy 13 or 18) and has led to a 40% reduction in invasive prenatal testing procedures. LBs can also diagnose infectious diseases and help manage conditions like sepsis and tuberculosis.

Clinical application of LBs in the cancer space can be grouped into four categories:

- Optimal treatment selection and real-time monitoring of response to treatment (prognosis)
- Detection of recurrence after a period of remission or minimal residual disease detection
- Identification of treatment-resistance mechanisms that, once identified, may require a change in treatment strategy or even lead to the development of new target therapy drugs
- Screening and early detection for cancers, including MCED testing

> The use of MCED tests for cancer screening and detection is a rapidly developing field attracting significant interest and investment from government health agencies and insurance companies. While some liquid biopsies screen for a single cancer, MCED tests can detect biomarker signals from multiple cancers (up to 50 or more cancers) with a single blood draw.

Experience with MCED tests to date

The current recommendation for MCED tests is to conduct them in conjunction with, rather than instead of, currently recommended screening tests. Primary advantages of MCED tests include the following:

- Blood samples are generally easily obtainable and the sampling procedures are minimally invasive and quick and incur less pain and risk.
- The technology not only detects signals of possible cancer in the first instance in a non-invasive way, but also could determine the likely cancer site or tissue of origin (TOO).

CancerSEEK, which detects eight common cancers, was the focus of one of the early trials published in the MCED space. The test demonstrated reasonable sensitivity (ability to identify an individual who has cancer) and specificity (ability to designate an individual who does not have cancer), and accuracy for TOO detection was 63%. A follow-on feasibility and safety study of 10,000 women without cancer, in which positive test results were followed up with PET CT scans, showed 65% of detected cancers were at a localized or regional stage. The study reported no change in screening behavior and minimal unnecessary invasive diagnostic procedures performed due to false positive tests. The study concluded that CancerSEEK may be a feasible and safe test to complement standard-of-care screening.[3]

The three-part Circulating Cell-free Genome Atlas (CCGA) study trialed GRAIL's MCED test, Galleri. DNA methylation, the specific method of detection used by the Galleri test, enhanced tissue of origin (TOO) detection, resulting in an 88.7% TOO in true positives in the third validation CCGA study. Overall specificity of the Galleri test was 99.5%. While good, that amounts to 1 in 200 false positive test results. Overall sensitivity was 51.5%, meaning that approximately half of all cancers were detected. Having high sensitivity is important to ensure the test can detect low-volume, smaller tumors, but sensitivity was lower at earlier stages – 16.8% at stage 1, 40.4% at stage 2 – and higher at later stages – 77.0% and 90.1% for stages 3 and 4, respectively. Sensitivity also varied by cancer type, proving sub-optimal for breast cancer at 30.5%, but better for lung at 74.8%, colorectal at 82%, pancreatic at 83.7%, and ovarian cancer at 83.1%. This is significant as some in the latter group have no current screening modality, are more aggressive, are often detected late in the clinical course, and contribute significantly to current cancer mortality. Also of note, the Galleri MCED test detected cancer signals in more than 50 cancer types. [4,5,6]

PATHFINDER is the most recent Galleri trial result to be released. This prospective study of a screening population evaluates the clinical feasibility, or implementation of the test following a cancer signal-detected result, in those ≥50 years of age with and without risks over a 12-month follow-up period. The primary outcome identified length and extent of diagnostic testing required to confirm the presence or absence of cancer. Of the 6,621 adults over 50 with analyzable results and without symptoms suggestive of cancer, a cancer signal was detected in 92 of them (1.4%), of whom a cancer diagnosis was subsequently confirmed in 35 people (38%) – the true positives. The remaining 57 (62%) had no cancer diagnosis – the false positives. Median time required for diagnostic resolution was shorter in the true positives, and fewer procedures were performed on this group than on those with false positive results. Specificity of the test was 99.1%; standard screening in the study population identified 29 cancers. Further clinical utility studies to expand on these findings likely will follow.[7]

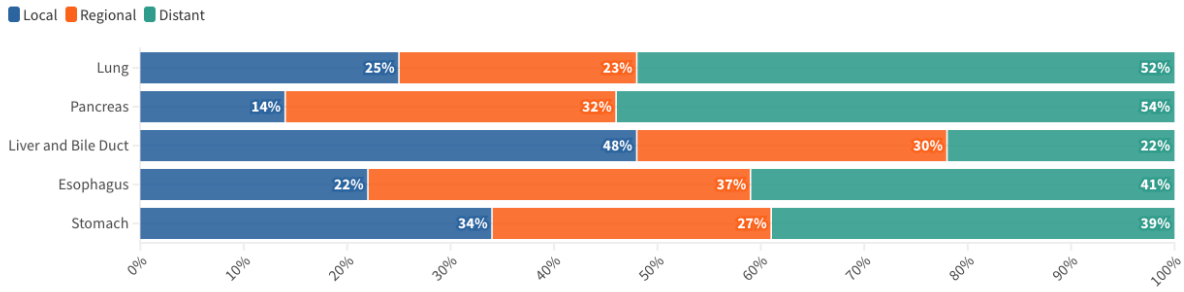
Opportunity for early detection

Traditional screening methods used today are already quite effective at diagnosing targeted cancers at earlier stages and have led to strong improvements in cancer mortality outcomes. However, the cancers primarily screened for today in the U.S. (breast, colorectal, prostate, and cervical cancer) make up less than a quarter of cancer deaths.[8] Screening of lung cancer is available but is limited and highly targeted with low take-up rates. The greatest potential for cancer mortality improvements lies in detecting cancers that currently go unscreened and are diagnosed at later stages and with poor prognosis. These include cancers such as lung, pancreatic, liver, esophagus, and stomach, which together made up about 20% of new cancer diagnoses in the U.S. in 2023 but almost 40% of all cancer deaths.[9] The five-year relative survival rate,[10] across all stages and by stage at diagnosis, for this group of cancers is, as expected, quite poor at around 24% but varies by cancer.

Figure 1: Five-year survival rates for cancers commonly diagnosed at later stages (U.S.)

Cancer Site	New Cases (2023)	Deaths (2023)	Five-Year Survival Rate			
			All Stages	Local	Regional	Distant
Lung	238,340	127,070	27%	62%	35%	8%
Pancreas	64,050	50,550	13%	46%	16%	3%
Liver and Bile Duct	41,210	29,380	21%	38%	14%	4%
Esophagus	21,560	16,120	23%	51%	26%	6%
Stomach	26,500	11,130	36%	74%	34%	7%
Total	**391,660**	**234,250**	**24%**	**57%**	**28%**	**7%**

Figure 2: Stage mix at diagnosis for cancers commonly diagnosed at later stages: 2011-2020 (U.S.)[11]



To estimate the potential for mortality improvements resulting from a "left shift" in the stage mix at which these cancers are diagnosed, consider a scenario in which MCED testing is used to detect some cancers at earlier stages. For example, the mix at the local and regional stages might move 5% higher, with a corresponding decrease at the distant stage, such as going from a 40/30/30 local/regional/distant split to 45/35/20.

Figure 3: MCED testing scenario: projected shift in five-year survival rates

Cancer Site	Five-Year Survival Rate (Today)	Five-Year Survival Rate (5% shift to earlier stages)	Improvement in 5-year Survival Rate
Lung	27%	31%	15%
Pancreas	13%	16%	21%
Liver and Bile Duct	21%	24%	11%
Esophagus	23%	26%	14%
Stomach	36%	41%	13%
Total	24%	28%	15%

This scenario projects an improvement of approximately 15% in the five-year survival rate and a 5% reduction in the overall cancer mortality rate.

Key assumptions to consider in modeling the impact of MCED tests

Actuaries need to consider the impact of emerging medical technology on future mortality and morbidity rates, particularly with insurance products that provide long-term guarantees. Models can test for a range of potential results, which is particularly important with some key assumptions having a large degree of uncertainty around them and with much yet to be learned regarding the real-world implementation of these tests.

Important assumptions to consider include the following:

- **Effectiveness.** What is the probability that an LB can detect a cancer where one exists? This is represented by the sensitivity of the test and, as we have seen, varies significantly by stage of cancer and site.
- **Uptake.** How widely will the tests be used in different age groups as part of population screening programs, what screening interval will be

recommended, and what proportion of the population will elect to screen themselves regularly?

- **Acceleration.** How much earlier will cancers be diagnosed by MCED tests relative to when they are diagnosed today by either traditional screening programs or via tissue biopsies and clinical investigations following symptoms?

Actuaries need to explore data and information available for each of these assumptions to develop an estimate and define potential sources of uncertainty in these estimates.

Effectiveness

Out of the three key assumptions, effectiveness has the most information available. Several studies have estimated the accuracy of MCED tests for TOO and at different stages.[12] These studies have found that the tests are generally effective, although it varies by cancer, and, importantly, that the tests are more effective at later stages. Any model therefore needs to allow for different effectiveness assumptions by site and stage of cancer.

The effectiveness of MCED tests likely also will improve in the future as additional data obtained through further clinical studies improves the tests' ability to detect more cancers earlier. Future estimates of this assumption are uncertain and should be sensitivity-tested, as part of optimistic and pessimistic scenario modeling, for example.

Uptake

It is uncertain if, when, and how quickly MCED tests will be adopted as part of large-scale population screening programs. That likely also will vary by geography. Clinical trials are now underway to gather more data and evaluate the effectiveness and feasibility of the tests. It is reasonable to expect the uptake of MCED tests will grow slowly over time, depending on several factors. Modelled assumptions therefore should vary by calendar year and consider the following:

- Scalability of the technology

- Costs, and whether economies of scale bring down the cost of these tests, particularly when provided as part of government-sponsored healthcare screening
- Regulatory approvals and government health departments' inclusion of MCED tests as part of recommended screening programs
- Behavioral factors such as consumer comfort with the tests relative to current screening tests and data and privacy concerns around the use of genetic material

In setting the uptake assumption, current screening rates can serve as a guide; however, considerable subjectivity remains, depending on views of relevant factors and the scenario being considered. As such, current screening rates can help set the long-term uptake assumption in one of two ways:

- As a floor in an optimistic scenario – the tests are cost effective, rolling out the tests at scale is successful, and the less invasive nature of the tests drives uptake
- As a ceiling in a more conservative scenario – uptake is strong but not expected to surpass current screening uptake due to behavioral factors, costs, and healthcare capacity

Another consideration is how the uptake will vary by age. Again, current screening rates can be used as a guide to gauge which age groups likely will be targeted with MCED test screening programs.

Sensitivity testing using a variety of scenarios is crucial given the current uncertainty about how the rollout of MCED tests will occur.

Acceleration

Acceleration assumptions capture expectations around how much earlier LBs will diagnose cancers compared to traditional screening or investigation of patient symptoms. Acceleration presents two impacts to consider in a model:

- Cancers diagnosed earlier can be treated earlier and thus likely would respond better to treatment, improving mortality outcomes.

- Diagnosing cancer at an earlier stage increases survival rates, given current mortality outcomes by stage.

The mortality improvements attributable to each of these are difficult to determine. One approach is to determine the number of years of acceleration expected, which likely varies by cancer:

- Currently screened cancers already are diagnosed quite early, given the success of traditional screening programs, resulting in limited acceleration potential from the introduction of LB tests for these cancers, compared to the greater opportunity for acceleration among unscreened cancers.
- More aggressive cancers that, on average, progress more quickly have a shorter window for acceleration, relative to cancers that on average progress more slowly.

By expressing acceleration periods in years, it is possible to compare against typical progression times between stages to estimate the probability of accelerating diagnosis to an earlier stage. If the acceleration period in years is higher than the progression time between stages, then accelerating to an earlier stage is more likely.

The acceleration period also can inform assumptions around the mortality improvements from earlier diagnosis without acceleration to an earlier stage, for instance via an assumption that allows for cancer mortality reduction proportional to the number of years of acceleration. The subjectivity and uncertainty in setting this assumption can be mitigated by leveraging medical expertise and employing sensitivity testing.

A new model for assessing the impact on future mortality and morbidity

RGA has built a model to assess the impact of MCED tests on cancer morbidity and mortality in future calendar years.

Morbidity impact

In modeling the impact on cancer morbidity rates, our approach was to shift a portion of incidence from older ages to younger ages, where the

proportion of incidence accelerated depends on the assumptions discussed above and include:

- The uptake or percentage of people at a given age screened via MCED tests
- The effectiveness and probability that the MCED test detects a cancer, which varies by site and stage at diagnosis
- The acceleration period, or the number of years that the diagnosis is accelerated, which determines the new age at which the incidence occurs

As these assumptions change over time, the proportion accelerated relative to current incidence rates would change.

It is also important to consider the overdiagnosis of cancer, a common feature of all early cancer screening programs. This represents cancer incidence that would not have been diagnosed previously, as the cancer was asymptomatic, was slow to progress, and had no impact on mortality of the life. As MCED tests are rolled out, more of these incidental cancers will be detected and could be eligible for living benefits claims under a critical illness policy. An increase in incidence rates therefore should proportionally reflect the rate of overdiagnosis expected by cancer site and the uptake and effectiveness of LBs. With the effectiveness of LBs currently lower for early-stage cancers, the amount of cancer overdiagnosis should be limited initially.

The probability of acceleration to earlier stages also should be considered, given its impact on cancer mortality rates. This is also important if modeling impacts on staged cancer products, where cancers diagnosed at earlier stages may be eligible for only partial benefits. This expected acceleration in the stage mix and lower benefit payment could offset claim acceleration to younger ages for staged cancer products.

Mortality Impact

To model the impact on mortality business, cancer deaths can be compared under two scenarios:

- Baseline (Status Quo) Scenario. Cancers are diagnosed in the future as they are diagnosed today, through either traditional screening or symptomology.
- MCED Scenario. MCED tests are gradually rolled out to the wider population as part of national screening programs. The speed and extent of the rollout largely are reflected by the uptake assumption described above.

Under each scenario, cancer incidence by stage is projected for future years, with the MCED scenario reflecting a slowly improving stage mix over time due to the acceleration of diagnosis. Cancer deaths from each year of incidence also are projected forward, using mortality after diagnosis by stage curves from current cancer survival data. The projected cancer deaths can then be compared across both scenarios to get a view of potential improvement in cancer mortality resulting from MCED tests' rollout.

Results

RGA's model projected MCED tests' impact on mortality and morbidity rates in three countries: the U.S., the U.K., and Hong Kong – across a number of scenarios. Results indicate significant impacts on cancer incidence and mortality rates over the next 20 years, with these impacts growing over time largely in line with the uptake assumed in a given scenario.

> The model projects a material increase in incidence rates over the next 20 years for the ages where screening rates are expected to be the highest (ages 45-70) due to acceleration of diagnosis to younger ages.

The results across all ages show a slight increase in incidence rates – up to 4% across the modelled countries and scenarios – corresponding to the expected increase in the rate of overdiagnosis. Looking across cancers, those not currently screened see the highest accelerations and also the greatest levels of overdiagnosis.

Results from mortality impact modeling suggest a tangible reduction in mortality rates, with the greatest reductions in cancer mortality occurring at the ages with the highest expected screening rates. Looking across various cancers, projected impacts are highest among the anatomical sites that are currently not screened and have the highest mortality differentials across stages, offering greater opportunity for mortality improvement through early diagnosis. Cancers currently diagnosed at later stages with worse mortality outcomes experience significant accelerations in the stage mix, leading to strong expected improvements in mortality.

It is important to recognize, however, that large uncertainties remain at present, particularly in relation to the rollout and uptake of this technology and the cost of the tests. A wide range of potential results reflects these uncertainties

Screening challenges and early results

The potential challenges MCED testing may pose, particularly for the insurance industry, deserve further consideration.

Screening for disease and disease risk has its own caveats and consequences. This includes the risk of overdiagnosis and increase in cancer incidence rates, as already discussed. Overdiagnosis can lead to overtreatment; conversely, it is still unclear how clinicians should manage detection of cancers with no effective treatment. Most studies to date on MCED testing have been case control studies, so the performance of the testing in the general population remains unknown. Insufficient clinical verification and validation prevent determining with confidence whether what is being detected is clinically meaningful, specifically in terms of improving survival or quality of life. The results of randomized prospective studies analyzing the effect of LBs on clinical outcomes and survival are currently lacking.

Many different types of tests exist – it is not “one size fits all” – and they have different sensitivity, specificity, and positive and negative predictive values. It remains unclear whether MCED testing meets the criteria for a good screening test, or indeed how frequently the screening should be carried out. Also currently unknown are the appropriate diagnostic procedures or medical evaluations that should follow a so-called “hit” or positive MCED

test. The full extent of the possible benefits and harms of using MCED tests for cancer screening are not yet known, and a cost-benefit analysis of performing the tests has yet to be carried out.

> Anti-selection and behavior risk also should be considered, especially if the cost drops and tests are offered outside of healthcare systems. Given that most liquid biopsies are considered genetically based assays as they detect genetic material, regulators' views on their use in the insurance space must be considered. Regardless, insurers will need to quantify potential impacts on cancer mortality and morbidity as liquid biopsy use increases within the clinical cancer screening sphere.

Health equity is another critical consideration with respect to MCED access, education, trust, and cost. While blood-based testing certainly has its advantages in addressing some of these, it may not solve all health equity issues. Studies need to address inclusivity in terms of performance and impact across different population groups, with an ability to perform robust sub-analysis.

While many unanswered questions remain, it is worth noting that in September 2021, the U.K.'s National Health Service (NHS) launched the world's largest randomized clinical trial of an MCED test (NHS-Galleri trial). The study is piloting Galleri with 140,000 asymptomatic, older-age volunteers. The hope is to detect 75% of cancers at early stages – the current detection of cancers at stage 1 and 2 in the U.K. accounts for 55% of all detected cancers.[13]

A second part of the research initiative (SYMPLIFY trial) will evaluate Galleri's performance in a high-risk group of symptomatic patients referred for further work-up owing to a suspicion of cancer. The goal: to see whether the Galleri MCED test could support faster diagnosis in these patients. In June 2023, the first analysis showed promising results: 368 patients of the 5,461

evaluable patients were diagnosed with cancer through standard-of-care screening. The Galleri test detected a cancer signal in 323 people – two thirds (244) of whom were diagnosed with cancer – and detected the TOO in 85% of those cases. Overall, Galleri identified 66% of the patients who were subsequently diagnosed, with a false positive rate below 2%.[14]

Further motivation for carrying out these trials stems from MCED tests' potential to provide wider accessibility to cancer screening, improved referral rates, and improved patient experience in general, as well as to address social, economic, and racial inequalities in access to cancer diagnosis and care. Further rollout through the NHS is expected to expand to one million people during 2024, if the initial trial is deemed successful.

In June 2021, GRAIL launched Galleri in the U.S. It is currently available only by prescription for people aged 50 and older. The test is not currently FDA approved but was introduced as a Laboratory Developed Test (LDT), an FDA category for tests developed and used in a single laboratory as a screening tool.

Additional considerations

As mentioned, LBs also present the potential for overdiagnosis and overtreatment[15] of cancers that, if left untreated, would have been unlikely to cause symptoms or death. This overtreatment may lead to unnecessary or potentially harmful treatment (medications, surgery, invasive tests) of cancers that would not have impacted mortality otherwise. The mental health impact of overdiagnosis should also be considered as studies have shown increased risk of depression, anxiety, and even suicide following a cancer diagnosis.[16]

There is also the risk of false negative tests, and a person who receives a false negative may delay seeking medical care even if they have symptoms. Meanwhile, a high false positive rate (low specificity) could lead to unnecessary investigations that are potentially invasive, harmful, and burdensome to healthcare systems.

Summary and Conclusions

Advances in medical technology make up one of many drivers that will impact future mortality and morbidity rates. Promising technologies like MCED testing are likely to be used in some way in the future, given the potential favorable impact they could have on population mortality and healthcare costs. Insurance companies should consider MCED testing's potential impact now, especially for products with long-term premium rate guarantees and with high exposure to mortality or longevity and morbidity risk. Assumptions and modeling methods can then be refined over time as more is learned about the real-world applications of these tests.

> Modeling and quantifying the impact of MCED testing is complex and the results should be considered carefully, with an understanding of how an insurer's current mortality and mortality trend assumptions already account for historical improvements in cancer screening and treatment and where LBs fit in as an additional driver. Insurance companies should monitor clinical trials and the ongoing progress and adoption of MCED tests to evaluate whether developments align with the insurer's expectations, particularly in modeling impacts on mortality and morbidity.

Additional risks insurers should consider include:

- Regulatory uncertainty: How results of these tests and insurers' use of them may be regulated remains unclear, especially as LBs do generally use genetic material to detect cancers.
- Data and privacy concerns: Concerns around the data gathered by tests, how it will be shared with the insurer and third parties, and consumer comfort with the entire process must be taken into account.

- Anti-selection risk: Individuals may test themselves for cancer signals via LBs and proceed to anti-selectively purchase new or additional insurance or avoid lapsation without disclosing this to an insurance company.

Beyond risks, there are also opportunities to explore:

- Insurers could potentially offer these tests as a value-added service to enhance relationships with customers.
- Insurers could potentially improve underwriting comprehensiveness by incorporating LBs as part of the application process for products where a blood draw is already taken, assuming this and this use is allowed by regulators.

At RGA, we are eager to engage with clients to better understand and tackle the industry's most pressing challenges together. Contact us to discuss and to learn more about RGA's capabilities, resources, and solutions.

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References

1. https://www.nature.com/articles/s41392-021-00817-8
2. https://www.labce.com/spg1580026_the_cellsearch_ctc_test.aspx#:~:text=The%20system%20was%20initially%20approved,for%20monitoring%20metastatic%20prostate%20cancer
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6080308/
4. https://www.annalsofoncology.org/article/S0923-7534(20)36058-0/fulltext
5. https://www.annalsofoncology.org/article/S0923-7534(21)02046-9/fulltext
6. https://grail.com/wp-content/uploads/2020/12/Fact-Sheet-The-Circulating-Cell-free-Genome-Atlas-CCGA-Study.pdf
7. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01700-2/fulltext
8. https://seer.cancer.gov/statfacts/html/common.html
9. https://seer.cancer.gov/statfacts/html/common.html
10. https://seer.cancer.gov/statistics-network/explorer/application.html site=18&data_type=4&graph_type=2&compareBy=stage&chk_stage_104=104&chk_stage_105=105&chk_stage_106=106&chk_stage_107=107&relative_survival_interval=5&sex=1&race=1&age_range=1&advopt_precision=1&advopt_show_ci=on&hdn_view=1&advopt_show_apc=on&advopt_display=1#resultsRegion1
11. https://seer.cancer.gov/statistics-network/explorer/application.html?site=18&data_type=1&graph_typ

e=4&compareBy=sex&chk_sex_1=1&race=1&age_range=1&advopt_precision=1&hdn_view=1&advopt_show_apc=on&advopt_display=2

12. https://www.annalsofoncology.org/article/S0923-7534(21)02046-9/fulltext
13. https://www.nhs-galleri.org/
14. https://www.cancer.ox.ac.uk/research/projects/symplify
15. Liquid Biopsy: Using Tumor DNA in Blood to Aid Cancer Care - NCI

Depression and anxiety among people living with and beyond cancer: a growing clinical and research priority | BMC Cancer | Full Text (biomedcentral.com)